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Publication Date

2018-11-01

DOI

10.1016/j.clinbiochem.2018.09.007

Peer reviewed

Clinical Biochemistry 61 (2018) 18–22

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Multicenter assessment of a hemoglobin A1c point-of-care device for diagnosis of diabetes mellitus

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ARTICLE INFO

Keywords:
HbA1c
Point-of-care
Diabetes
NGSP

ABSTRACT

Objective: A multisite investigation compared the analytical performance of a point-of-care (POC) HbA1c device with multiple commonly used HbA1c laboratory methods and an NGSP (National Glycohemoglobin Standardization Program) reference method.

Research Design and Methods: The Afinion AS100 POC device analyzed HbA1c using 618 EDTA whole blood excess patient specimens with clinically indicated HbA1c testing. Results were compared to measurements across five clinical laboratories and the NGSP reference method. Precision was evaluated over 8–10 consecutive days for low-, mid-, and high-range HbA1c specimens at all five sites.

Results: Over a wide range of HbA1c values (4.0%–15% HbA1c), 97.1% of the POC results and 94.5% of routine laboratory results fell within the target value of ± 6% of the NGSP reference method results. The POC HbA1c results at 6.5% exhibited a total relative bias of −0.6% (−0.04% HbA1c) compared to the reference method while the aggregate of laboratory methods displayed a relative bias of −0.9% (−0.06% HbA1c). The total imprecision of the POC results ranged from 0.74–2.13% CV across the analytic measurement range compared to 0.81–3.23% CV for the routine laboratory methods.

Conclusions: The accuracy and precision of the Afinion POC HbA1c method was comparable to the laboratory HbA1c methods supporting the FDA's recent approval of the Afinion HbA1c Dx device for use in the diagnosis of diabetes.

1. Introduction

Diabetes is a significant global public health concern, with an estimated mortality rate of over 1.5 million lives per year [1]. Diabetes is a chronic condition that results from autoimmune related insulin deficiency (type 1) or insulin resistance/β-cell dysfunction (type 2), with type 2 diabetes comprising a majority of diabetes cases and new diagnoses. Type 2 diabetes results from chronic hyperglycemia that leads to insulin insensitivity at the cellular level and ultimately the inability to adequately metabolize dietary glucose [1,2].

Hemoglobin A1c (HbA1c) is formed via non-enzymatic glycation on the terminal valine of the β-globin chain. The concentration of HbA1c is highly dependent upon the average lifespan of the red blood cell and blood glucose concentrations, but is representative of an individual's average blood glucose concentration over the last 2–3 months [3,4]. Therefore, monitoring HbA1c concentrations are beneficial for assessing long-term glycemic control. Clinical guidelines from the American Diabetes Association, World Health Organization, and the International Diabetes Federation recommend that a HbA1c cutoff ≥6.5% (48 mmol/mol) can be utilized for the diagnosis of diabetes, if testing is conducted

Abbreviations: Hb, hemoglobin; HbA1c, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial; POC, point-of-care; SOC, standard-of-care; EDTA, ethylenediaminetetraacetic acid; IRB, Institutional Review Board; RMP, reference method procedure; TAE, total allowable error; CV, coefficient of variation; RMS, root mean square

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https://doi.org/10.1016/j.clinbiochem.2018.09.007
Received 19 July 2018; Received in revised form 14 September 2018; Accepted 16 September 2018
Available online 17 September 2018
0009-9120/ Published by Elsevier Inc. on behalf of The Canadian Society of Clinical Chemists.

using an assay which is standardized and certified by the National Glycohemoglobin Standardization Program (NGSP) and traceable to the Diabetes Control and Complications Trial (DCCT) reference method [1,2,5]. Recently, the FDA has cleared the Abbott (formerly Alere) Afinion AS100 HbA1c Dx device as a moderately complex test for use in the diagnosis of diabetes, which is a first for a point-of-care (POC) HbA1c method.

Historically HbA1c point-of-care (POC) devices demonstrated significant bias and variability when compared to non-POC assays, which led to clinical guideline recommendations against utilization for diagnostic purposes [6–9]. However, there have been improvements in HbA1c assays and technologies over time and further investigation into the accuracy and precision of these devices is required. POC HbA1c measurements could expedite diagnostic decisions and medical interventions provided they meet performance standards [6]. The purpose of this multicenter study was to evaluate the analytical performance of HbA1c using the Afinion AS100 POC analyzer between multiple sites, and compare the performance characteristics to other frequently used automated HbA1c assays and an NGSP reference method.

2. Materials and methods

2.1. Instrumentation

The analytical performance of the Afinion AS100 POC analyzer (Alere Technologies AS) was compared to three clinical laboratory HbA1c platforms (Roche Tina-quant® HbA1c Gen. 3, Bio-Rad Variant II Turbo, Siemens Dimension Vista) across five clinical laboratories, and with an NGSP reference laboratory (Secondary Reference Laboratory #9, Tosoh G8 automated glycohemoglobin analyzer) (Table 1). The Afinion AS100 is a POC instrument that quantifies HbA1c in capillary or venous blood using boronate affinity methodology, which is highly specific for 1,2-cis diols to measure total glycohemoglobin that is then converted and reported as HbA1c. A single lot of test cartridges and control materials was used for the study. The Roche Tina-quant® HbA1c Gen. 3, used at two sites, and the Siemens Dimension Vista® HbA1c, used at one site, are both turbidimetric inhibition immunoassays (TINIA). The Bio-Rad Variant II Turbo, used at two sites, employs cation exchange HPLC for direct measurement of HbA1c. The Roche and Bio-Rad HbA1c assays are FDA-cleared for use as an aid in the diagnosis of diabetes. The HbA1c reference method procedure (RMP) was performed at the Diagnostic Diabetes Laboratory (DDL) in Columbia, MO on the Tosoh G8 automated glycohemoglobin analyzer, which measures HbA1c by cation exchange HPLC. The Tosoh G8 in the DDL is part of the NGSP network.

If the POC HbA1c values differed by > 10% from the reference method, specimens were reflexed for confirmatory testing at the DDL using alternative NGSP certified boronate affinity methods (Ultra^2 and Premier Hb9210 HbA1c Analyzers, Trinity Biotech).

2.2. Study design

De-identified, remnant EDTA anti-coagulated whole blood specimens with clinical orders and indications for HbA1c testing were utilized for this study. The study began in June 2016 and completed in June 2017. Each institution involved had the protocol reviewed and approved by its local Institutional Review Board (IRB) before participation in the study was allowed. HbA1c was analyzed using the local laboratory methods and the POC device at all five clinical sites. Specimens were refrigerated after the initial laboratory measurement and analyzed using the POC instrument within 72 h after collection. Specimens were excluded from POC and routine laboratory measurements if they were previously frozen or were known to have > 5% Hemoglobin F (HbF) present. After routine laboratory and POC measurements were performed, aliquots of each sample were frozen within 72 h of initial collection and stored at ≤ −70 °C prior to shipping to the NGSP reference laboratory for analysis.

The accuracy of the Afinion HbA1c Dx test was assessed at each site by evaluating a minimum of 120 specimens evenly distributed across the low (4.00–6.00% HbA1c), mid (6.01–7.00% HbA1c) and high (7.01–15.00% HbA1c) range for HbA1c. Results were compared to routine clinical laboratory methods and to the NGSP reference method.

Precision of the POC device relative to each laboratory method was conducted and evaluated independently at each site using three EDTA whole blood specimens (one specimen at each target HbA1c value). Each site independently created their own pools for low, medium, and high HbA1c at similar nominal concentrations. Each specimen was analyzed in duplicate in the morning and again in the afternoon, for a total of 4 measurements per day by each laboratory's and POC methods over 8–10 consecutive days.

3. Results

3.1. Accuracy of POC and laboratory HbA1c values to RMP

A total of 618 patient specimens were analyzed between the POC and all laboratory methods. The Deming regression demonstrated a strong correlation (Pearson $R = 0.994$) between the Afinion HbA1c values and the Tosoh G8 reference method values (Fig. 1A). The mean of laboratory sites HbA1c also displayed a strong correlation (Pearson $R = 0.989$) with the reference method values (Fig. 1B).

Table 2 shows the total biases of the AS100 results, the aggregate mean of all local laboratory method results, and individual laboratory method results at 5%, 6.5%, and 8% HbA1c compared to the reference method (SRL#9-Tosoh G8). The current NGSP requirement for total allowable error (TAE) is ± 6% across the measurement range manufacturer certification requires that 37/40 (92.5%) of results must be within ± 6% of the SRL [10]. 600 of 618 POC results (97.1%) and 584 of 618 laboratory results (94.5%) were within ± 6% TAE when compared to the reference method. Within the mid-range (6.01–7.00% HbA1c) of HbA1c and near the diagnostic decision point (6.5% HbA1c),

Table 1
Local laboratory methods of participating clinical laboratories.

Site	Clinical laboratory	Laboratory method	Test principle
1	University of California, San Diego (UCSD)	Roche Tina-quant® HbA1c Gen. 3*	Turbidimetric inhibition immunoassay
2	Washington University (WashU)		
3	University of Minnesota (UMN)	Siemens Dimension Vista	
4	University of California, San Francisco (UCSF)	Bio-Rad Variant II Turbo HbA1c*	Cation-exchange HPLC
5	Hennepin Country Medical Center/Minneapolis Medical Research Foundation (MMRF)		
N/A	Diabetes Diagnostic Laboratory (Columbia, MO)	Tosoh G8 Automated Glycohemoglobin Analyzer*,[a]	
		Ultra^2* and Premier Hb9210*,[a]	Boronate Affinity

* FDA cleared for diagnosis.
[a] NGSP certified reference method.

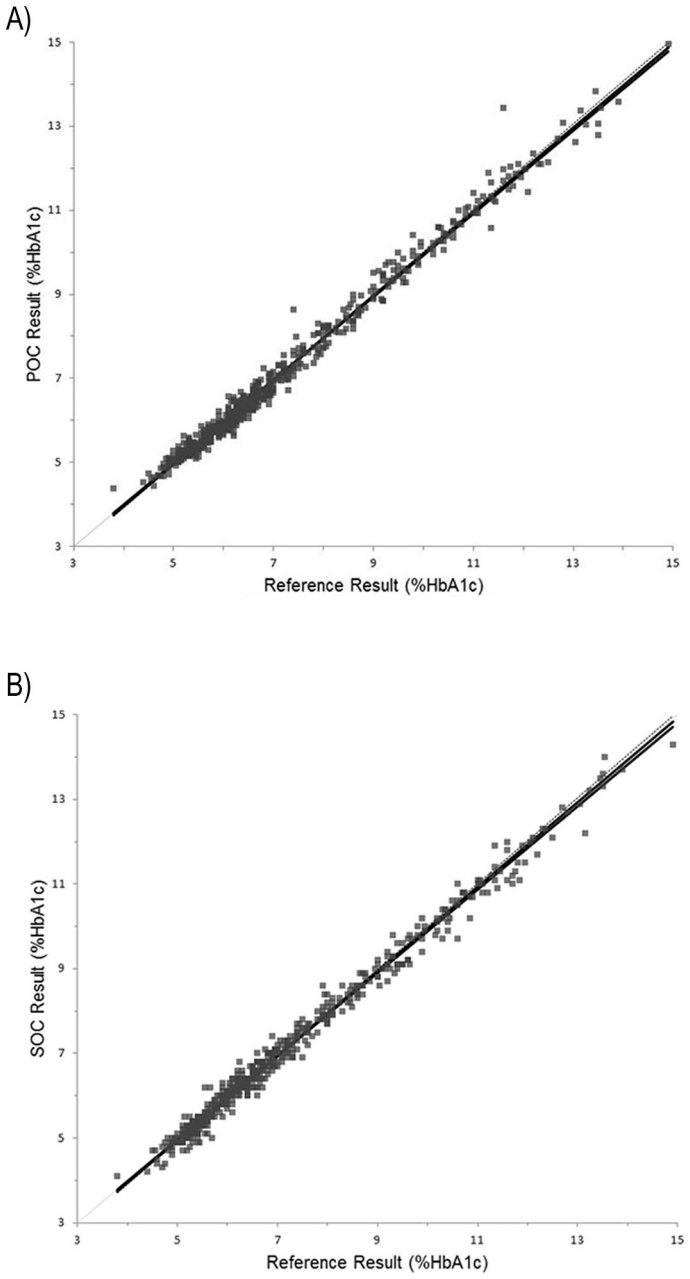

Fig. 1. Accuracy-weighted Deming regression plots for (a) POC and (b) routine laboratory standard-of-care (SOC) methods compared to the NGSP reference method (Tosoh G8).

Table 2
Accuracy-weighted Deming regression results compared to the NGSP reference method. Units are meant to indicate a relative % of the measured value. 95% Confidence intervals are shown in [ ].

	Afinion AS100	Aggregate mean of laboratory methods	Tina Quant Gen.3	Variant II turbo	Dimension vista
Count	618	618	247	241	130
Intercept	−0.06 [−0.14,0.02]	−0.06 [−0.14,0.03]	−0.15 [−0.29, −0.01]	−0.05 [−0.19,0.1]	0.19 [0.03,0.35]
Slope	1.003 [−0.99,1.02]	1.000 [0.99,1.01]	1.008 [0.99,1.03]	1.002 [0.98,1.03]	0.969 [0.94,0.99]
Pearson R	0.994	0.989	0.993	0.984	0.994
Bias at 5% HbA1c	−0.9% [−1.38%, −0.45%]	−1.1% [−1.61%, −0.65%]	−2.3% [−3.1%, −1.4%]	−0.8% [−1.36%, −0.19%]	−0.7% [−0.21%,1.63%]
Bias at 6.5% HbA1c	−0.6% [−0.86%, −0.39%]	−0.9% [−1.18%, −0.58%]	−1.6% [−1.97%, −1.14%]	−0.5% [−1.26%,0.46%]	−0.2% [−1.35%, −0.08%]
Bias at 8% HbA1c	−0.5% [−0.76%, −0.15%]	−0.7% [−1.13%, −0.31%]	−1.1% [−1.61%, −0.62%]	−0.4% [−1.26%,0.46%]	−0.7% [−1.35%, −0.08%]

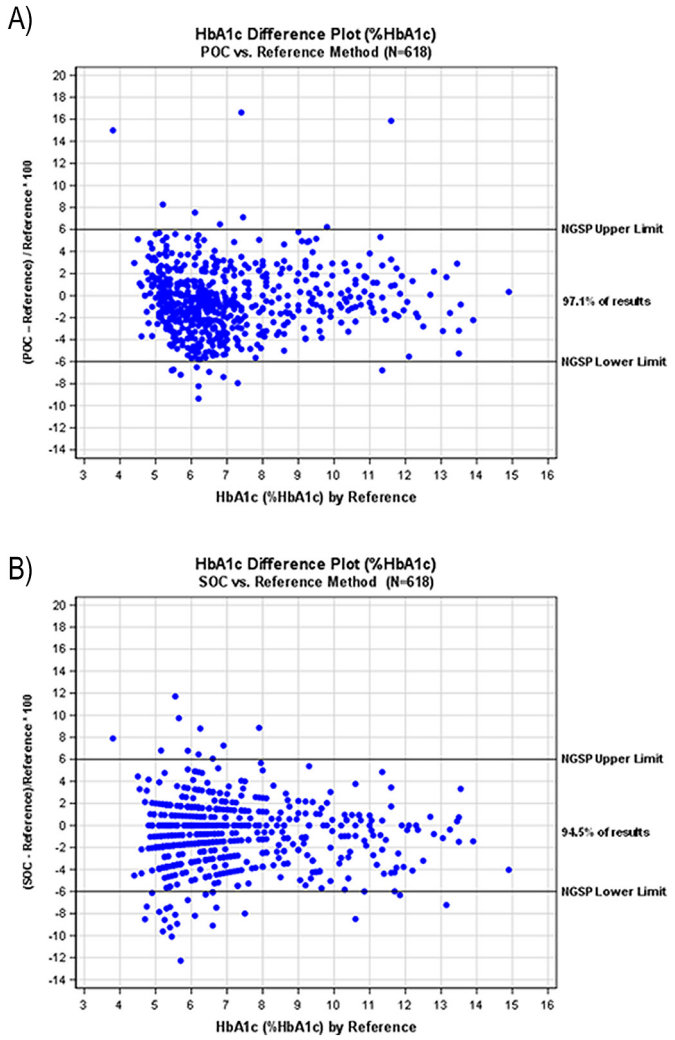

Fig. 2. Difference plots comparing point of care (POC) and routine laboratory standard-of-care (SOC) HbA1c results with an NGSP reference method. Limit lines of ± 6% are illustrated on the graph. (a) The POC device versus the mean results from the reference method. (b) SOC laboratory result versus the mean reference method result.

193 of 200 POC values (96.5%) and 190 of 200 laboratory values (95.0%) were within ± 6% TAE limits. Absolute bias of the 7 POC results in the mid-range that had a relative bias > 6% ranged from −0.58% HbA1c to +0.46% HbA1c when compared to target reference values. Absolute bias of the 10 laboratory HbA1c results in the mid-range that had a relative bias > 6% ranged from −0.6% to +0.6% when compared to the target reference values.

Difference plots comparing the HbA1c results of the POC and routine laboratory methods to the average of duplicate HbA1c values analyzed at the NGSP reference laboratory are displayed in Fig. 2. Both plots indicate minimal proportional and constant error for both the POC and routine laboratory methods in comparison to the reference method. At the HbA1c diagnostic decision point of 6.5%, the POC results exhibited a total bias of −0.6% (e.g. an absolute bias of −0.04%HbA1c) compared to the reference method while the aggregate of laboratory methods displayed a total bias of −0.9% (e.g. an absolute bias of −0.06%HbA1c).

3.2. Precision

Table 3 displays the total imprecision (%CV) of the POC device over 8–10 days for low-, mid-, and high-range specimens (mean HbA1c values = 5.3%, 6.5%, 9.8%, respectively) with %CVs of 1.46%, 1.35%, and 0.85% respectively with data combined between all five sites, and varied from 0.97% to 1.85% at individual sites. The Roche mean HbA1c values were 5.2%, 6.6%, and 9.2% with calculated %CVs of 1.89%, 1.28%, and 1.55%, respectively, when combined across the two laboratories using the Roche method. The BioRad mean HbA1c values were 5.4%, 6.6%, and 11.5% with calculated %CVs of 2.39%, 1.87%, and 0.83%, respectively, across the two BioRad sites. The Siemens method, used at one site, had mean HbA1c values of 5.1%, 6.7%, and 8.5% with %CVs of 3.23%, 1.96%, and 1.44%, respectively.

4. Discussion

This multicenter analytical trial demonstrates equivalent or superior performance of the Alere Afinion POC HbA1c device compared to routine clinical laboratory HbA1c assays currently employed in the diagnosis of diabetes. These results are specific to the Afinion POC HbA1c method when performed in a laboratory setting and are in accordance with previously published results [11]. The Afinion device had stronger linear correlation (Pearson R) than the aggregate of laboratory methods with less bias and improved precision across the analytical measurement range, further strengthening the potential utility of the Afinion AS100 for diagnosis and monitoring of diabetes.

Three specimens tested by the POC device (Fig. 2A) had HbA1c results (mean A1c of 4.4%, 8.6% and 13.4%) that differed by > 10% relative to the NGSP reference method (mean A1c of 3.9%, 7.4%, and 11.6%). Repeat analysis of these specimens using an NGSP certified boronate affinity method yielded results that were in close agreement (within 3%, e.g. 0.3% HbA1c at an HbA1c of 8.6%) compared to the POC HbA1c results. These results suggest that the discrepancies in HbA1c values between POC and the reference measurements in these three outliers were likely due to differences in methodologies as the two methods based on boronate gave near identical results. For these three specimens the differences in results appears to be due to differences between boronate affinity and the direct measurement of HbA1c via ion-exchange chromatography, and is not specific to the POC method.

Due to challenges in obtaining a fasting plasma glucose in some patients, an FDA cleared POC HbA1c device that demonstrates comparable accuracy and precision to common laboratory platforms with claims for diagnosis of diabetes has considerable clinical utility. The ability to provide rapid, accurate HbA1c results to at-risk populations using a POC device has the potential to further enable clinicians and caregivers to appropriately diagnose, monitor and implement effective therapies in patients with diabetes and reduce the risk of loss to follow-up care.

In summary, the data here demonstrates that the analytical performance of the Afinion POC HbA1c device is equivalent to a variety of common laboratory methods across multiple laboratories. These data support the recent FDA decision clearing the Afinion HbA1c Dx device as substantially equivalent to routine clinical laboratory methods allowing it to be used in the diagnosis of diabetes.

Acknowledgements

The authors acknowledge the contribution of Alere Inc. in designing the multisite investigation, providing the Afinion AS100 point-of-care instruments to each laboratory participating in this study, and performing statistical analysis of the study results.

Duality of interest

No conflicts of interest relevant to this article were reported.

Author contributions

B.E.S. and P.M.S. conducted and oversaw the study at the University

Table 3
Between day and between run precision for each HbA1c method.

Laboratory method	HbA1c range	Mean (% HbA1c)	Between day RMS CV	Between run RMS CV	Within run RMS CV	Total RMS CV	Number of sites	Number of observations
Variant II Turbo	Low	5.4	1.68%	1.39%	1.02%	2.39%	2	136
	Medium	6.6	1.61%	0.80%	0.60%	1.87%	2	140
	High	11.5	0.59%	0.18%	0.56%	0.83%	2	140
Tina Quant Gen. 3	Low	5.2	0.38%	0.48%	1.81%	1.89%	2	152
	Medium	6.6	0.00%	0.43%	1.23%	1.28%	2	152
	High	9.2	0.32%	0.80%	1.30%	1.55%	2	152
Dimension Vista	Low	5.1	1.27%	0.00%	3.23%	3.23%	1	72
	Medium	6.7	1.11%	0.82%	1.39%	1.96%	1	72
	High	8.5	0.77%	0.00%	1.27%	1.44%	1	72
Afinion AS100	Low	5.3	0.55%	0.47%	1.34%	1.46%	5	359
	Medium	6.5	0.55%	0.32%	1.24%	1.35%	5	363
	High	9.8	0.31%	0.13%	0.80%	0.85%	5	368

RMS, root mean square.

of California, San Diego Center for Advanced Laboratory Medicine under the guidance of R.L.F. A.K.S., K.S., F.S.A., M.G.S., and A.H.B.W. were responsible for conducting and overseeing the study at their respective laboratories. R.R.L. was responsible for overseeing the reference method at the DDL. B.E.S. and P.M.S. drafted the manuscript, and R.L.F., A.K.S., K.S., F.S.A., M.G.S., A.H.B.W., and R.R.L. edited and made significant contributions to the final draft of the manuscript.

References

[1] World Health Organization, Global Report on Diabetes, (2016) (ISBN 978 92 4 156 525 7.
[2] International Diabetes Federation Guideline Development Group, Global Guideline for Type 2 Diabetes, (2014), https://doi.org/10.1016/j.diabres.2012.10.001.
[3] I.M. Stratton, Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study, BMJ (2000), https://doi.org/10.1136/bmj.321.7258.405.
[4] J.W. Albers, W.H. Herman, R. Pop-Busui, E.L. Feldman, C.L. Martin, P.A. Cleary, B.H. Waberski, J.M. Lachin, Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study, Diabetes Care (2010), https://doi.org/10.2337/dc09-1941.
[5] American Diabetes Association, Standards of Medical Care in Diabetes - 2018, Diabetes Care (2018), https://doi.org/10.2337/dc18-Sppc01.
[6] L. Kennedy, W.H. Herman, Glycated hemoglobin assessment in clinical practice: comparison of the A1cNow point-of-care device with central laboratory testing (GOAL A1C Study), Diabetes Technol. Ther. (2005), https://doi.org/10.1089/dia.2005.7.907.
[7] K.L. Schwartz, J. Monsur, A. Hammad, M.G. Bartoces, A.V. Neale, Comparison of point of care and laboratory HbA1c analysis: a metronet study, J. Am. Board Fam. Med. (2009), https://doi.org/10.3122/jabfm.2009.04.090057.
[8] D. a Sicard, J.R. Taylor, Comparison of point-of-care HbA1c test versus standardized laboratory testing, Ann. Pharmacother. (2005), https://doi.org/10.1345/aph.1E504.
[9] A. St John, T.M.E. Davis, I. Goodall, M.A. Townsend, C.P. Price, Nurse-based evaluation of point-of-care assays for glycated haemoglobin, Clin. Chim. Acta. (2006), https://doi.org/10.1016/j.cca.2005.09.003.
[10] NGSP Protocol: Certification, http://www.ngsp.org/protcert.asp, (2010) , Accessed date: 16 July 2018.
[11] E. Lenters-Westra, R.J. Slingerland, Three of 7 hemoglobin a1c point-of-care instruments do not meet generally accepted analytical performance criteria, Clin. Chem. (2014), https://doi.org/10.1373/clinchem.2014.224311.